UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/753,079	01/08/2004	Bao-Lu Chen	PP18459.005	6553

27476 7590 05/03/2005

Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 05/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/753,079	CHEN ET AL.	
	Examiner	Art Unit	
	Yunsoo Kim	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/8,7/15,&9/23/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Yunsoo Kim, Group Art Unit 1644, Technology Center 1600

2. Applicants' response to the restriction requirement filed on 3/30/05 is acknowledged. Upon further consideration, the species election to TFPI variant is hereby withdrawn.

Therefore, claims 1-21 are under consideration in the instant application.

3. Applicants' claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

4. Applicants' IDS filed on 1/8/04, 7/15/04 and 9/23/04 have been acknowledged. As applicant failed to provide the copies of references, IDS filed on 7/15/04 has not been considered.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a lyophilized composition comprising of TFPI consisting of SEQ ID NO:1 or ala-TFPI, does not reasonably provide enablement for any TFPI comprising of SEQ ID NO:1 or TFPI variants comprising of at least 70% homologous to SEQ ID NO:1 or any fragments or TFPI analogs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use of the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in the art to practice the claimed invention.

The terms "comprising" or "comprises" in claims 1, 2, 7-9, 12, 14, 16, 18 and 20 are open-ended. It expands the amino acid sequence of SEQ ID NO:1 to include additional non-disclosed amino acids. As acknowledged in p. 9, [0038] and [0039] of the specification of the instant application, the TFPI analogs or variants include any addition of 100 or more amino acids and any TFPI variants range 20 amino acids of SEQ ID NO:1. Any fragments of 20 amino acids consisting of SEQ ID NO:1 do not even meet the limitation of 70% homologous to SEQ ID NO:1. The specification does not provide sufficient guidance as to which amino acid sequence within the polypeptide can be unique and retain a distinct functional capability of SEQ ID NO:1.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-494 in particular).

Therefore, there is insufficient direction as to how to make and to use a TFPI variant comprising any peptide sequence comprising of SEQ ID NO:1 by addition, at least 70% homologous peptides and fragments which can be used as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

Furthermore, Applicant has no working examples demonstrating peptide sequences which are at least 70% homologous to SEQ ID NO:1, analogs generated by addition of amino acids and TFPI variants of fragment size of 20 amino acids.

In view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to limit the claimed fragment to consisting of SEQ ID NO: 1 and ala-TFPI.

7. Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a lyophilized composition comprising TFPI consisting of SEQ ID NO:1 and ala-TFPI, however, applicant is not in possession of lyophilized compositions comprising a peptide comprising the SEQ ID NO:1, or a peptide sequence comprising at least 70% homologous to SEQ ID NO:1 or any TFPI analogs by addition of amino acids, or any TFPI fragment of 20 amino acids. There are $5.14x10^{45}$ possible combinations of amino acid sequences for at least 70% homologous to SEQ ID NO:1 alone.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-21 are rejected under 35 U.S.C. 103 as being unpatentable over Andya et al. (U.S.Pat. 6,267,958 B1) in view of Chen et al. (U.S.Pat. No. 5,888,968, IDS ref).

Andya et al. teach various stable lyophilized formulations comprising 50-600mM carbohydrate glass forming agent (i.e. 60mM trehalose, FIG.3-6, col. 3, lines 24-58), aqueous buffer formulation at pH 5.5-6.5, from 5mM to 600mM (i.e. 5mM histidine buffer at pH 6, Fig. 6, lines 50-57), crystal forming agent (i.e. mannitol), about 1% sucrose, about 4% mannitol and about 10mM histidine at pH 6 (table 2 on col. 22), sulfate (i.e. SDS, col. 15, lines 39-42) and phosphate buffer (col. 15, lines 3-10).

As Andya et al. define the "stable lyophilized" formulation as stable at 40°C for at least 6 months, the stable formulation is less than 3 % of aggregate present in the lyophilized formation, the reference teach the claimed properties of having 45% or greater aggregation stability and about 96% greater aggregation stability.

Given the molecular weight of 342g of sucrose and 182g of mannitol, concentrations in table 2 of reference meet the limitations of claims 16 and 17.

The claimed invention differs from the reference teachings by the recitation TFPI at a given concentration of 10mg/ml and formulation consisting of 10mM imidazole and 8.5% sucrose at pH 6.5.

However, Chen et al. teach the TFPI pharmaceutical composition at concentrations between 0.2mg/ml and 10mg/ml (abstract, claims 1-3) and a formulation consisting of 10mM imidazole and 8.5% sucrose at pH 6.5 (table 1, col.7, line 40).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to employ TFPI composition taught by Chen et al. in the stable lyophilized formulation taught by Andya et al. to increase, storage time and multi-use formulation (Andya, col. 1, lines 51-60).

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the stable lyophilized formulation taught by Andya et al. improves overall stability of protein and therapeutic application of formulation.

From the teachings of references, it would have been obvious to one of ordinary skill in art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yunsoo Kim
Patent Examiner
Technology Center 1600
April 22, 2005

Patrick, J. Nolan, Ph.D.
Primary Examiner
Technology Center 1600